

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
31 May 2001 (31.05.2001)

PCT

(10) International Publication Number
WO 01/37834 A1

(51) International Patent Classification⁷: **A61K 31/4439**,
9/48, 47/22

(21) International Application Number: PCT/IB00/01842

(22) International Filing Date:
22 November 2000 (22.11.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/166,761 22 November 1999 (22.11.1999) US

(71) Applicants and

(72) Inventors: **DEBOECK, Arthur, M.** [BE/US]; HC-02 Box
14885, Gurabo, Puerto Rico 00778 (US). **VAN DER BI-
EST, Francis** [BE/BE]; Keizerinlaan 56, B-1860 Meise
(BE). **BAUDIER, Philippe, R.** [FR/BE]; Rue Engeland
338, B-1180 Brussels (BE).

(74) Agent: **BEAUMONT, William, E.**; Oblon, Spivak, Mc-
Clelland, Maier & Neustadt, P.C., Fourth Floor, Crystal
Square Five, 1755 Jefferson Davis Highway, Arlington, VA
22202 (US).

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ,
DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR,
HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ,
NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM,
TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian
patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European
patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE,
IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF,
CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

- With international search report.
- Before the expiration of the time limit for amending the
claims and to be republished in the event of receipt of
amendments.

*For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.*

(54) Title: STABLE ACID LABILE BENZIMIDAZOLE PHARMACEUTICAL COMPOSITIONS

(57) Abstract: The present invention relates to a novel oral pharmaceutical stable formulation containing an acid labile benzimidazole compound, which is stabilized with a vitamin E derivative. More specifically, the composition comprises the acid labile benzimidazole compound in solution and/or suspension in oil and/or oil derivatives and a vitamin E derivative as stabilizer. A particular embodiment comprising omeprazole as acid labile benzimidazole compound and vitamin E Polyethylene glycol succinate as vitamin E stabilizer derivative is disclosed.

WO 01/37834 A1

Stable Acid Labile Benzimidazole Pharmaceutical Compositions

Summary of the invention

The present invention provides for a stable oral pharmaceutical composition containing an acid labile benzimidazole compound as active ingredient. The active ingredient in said formulation being stabilized with a vitamin E derivative.

The invention relates also to a cost effective manufacturing process for the preparation of said stable pharmaceutical dosage form. More particularly the manufacturing process comprises the filling in to gelatin and/or hydroxypropylmethylcellulose capsules of the mixed melted ingredients with the active drug. The capsules being thereafter optionally enteric coated.

Background of the invention

Acid labile benzimidazole compounds comprise 2-[2(pyridyl) methylsulfinyl] – benzimidazole or a derivative thereof (hereinafter sometimes referred to collectively as “benzimidazole compounds”) particularly the derivatives 2-[[3 methyl – 4 – (2,2,2 trifluoro methoxy) – 2 – pyridyl] methyl sulfinyl] benzimidazole and 5 – methoxy – 2 – [(4 – methoxy – 3, 5 – dimethyl – 2 – pyridyl) methylsulfinyl] benzimidazole which are useful as anti-ulcer agent. Those benzimidazole compounds, which are, described in US Patent: 4,255,431; 4,555,518; 4,753,955; 4,824,856; 5,171,746; 5,149,702; 5,215,974; 5,504,082; 5,703,097; 5,693,818; 5,840,910; 5,916,904; respectively, among others are known to have anti-ulcer activity, and/or useful for the treatment of glaucoma, and/or psoriasis and DNA viral infection.

These compounds have however extremely poor stability properties. They are susceptible to heat, moisture and light and their stability decreases with decreasing pH values. In dosage form i.e. tablets, powders, fine granules, granules and capsules, said compounds are apt to interact with other components contained in said dosage forms and accordingly are in less stable state as compared with the case where they occur alone. Thus, the content decreases and the color changes significantly during the manufacturing process of dosage form and with the lapse of time. Microcrystalline cellulose, polyvinylpyrrolidone (PVP), carboxymethylcellulose calcium, polyethylene glycol 6000 and Pluronic F68 (polyoxyethylenepolyoxypropylene copolymer), for instance are dosage form components adversely affecting the stability of said

compounds. Furthermore, in the case of coated tablets and coated granules among the above dosage forms, enteric coating bases such as cellulose acetate phthalate, hydroxypropylmethylcellulose acetate succinate and Eudragit (methacrylic acid-acrylic acid copolymer) have poor compatibility with said compounds and cause content decrease and color change. Nevertheless, one or more of these components or ingredients, which, as mentioned above, can produce adverse effects on the stability of said compounds, are essential in the manufacture of oral preparations and therefore difficulties are inevitably encountered in dosage form manufacture.

US Patent 4786505 describes a pharmaceutical preparation containing omeprazole together with an alkaline reacting compound or an alkaline salt of omeprazole optionally together with an alkaline compound as the core material, one or more sub-coating layer comprising inert reacting compounds which are soluble or rapidly disintegrating in water, or polymeric, water soluble filmforming compounds, optionally containing pH-buffering alkaline compounds and enteric coating.

US Patent 4853230 describes the same solution to the stability problem as patent 4786505 but extend it to all acid labile compounds.

US Patent 5093132 describes a stabilized pharmaceutical composition comprising: an effective amount of a 2-benzimidazole derivative selected from the group consisting of 2-benzimidazole and 5-methoxy-2-benzimidazole, or a pharmaceutically acceptable salt thereof; a basic inorganic salt stabilizing agent which is present in an amount effective to stabilize the composition, the benzimidazole derivative being in contact with the basic inorganic salt evenly; and an enteric coating for the composition.

US Patent 5385739 describes a stable formulation of omeprazole microgranules containing a neutral core consisting of sugar and starch, characterized in that it contains an active layer consisting of a dilution of omeprazole in mannitol in substantially equal amounts.

US Patent 5399700 describes a method for stabilizing an acid-unstable compound by forming an inclusion complex of omeprazole with cyclodextrin comprising: dissolving cyclodextrin in an aqueous alkaline solution at 40° to 70°C, and reacting said omeprazole with a cyclodextrin for 1 to 30 minutes in said alkaline solution, the ratio of said acid-unstable compound

to said cyclodextrin in said reaction being from about 1:1 to about 1:10, on a number of moles basis.

US Patent 5639478 describes a method of stabilizing an enteric coated anti-ulcer composition, which comprises: homogeneously admixing an effective amount of a 2-[(2-pyridyl) methylsulphanyl]-benzimidazole compound or a pharmaceutically acceptable salt thereof having a gastric acid secretion inhibitory property with a basic inorganic salt stabilizing agent; granulating the mixture; and enteric coating the granules.

All the above patents, try to solve the lack of stability of acid labile benzimidazole compounds in pharmaceutical composition by mixing them with inorganic basic salts. Nevertheless the processes therein describe require multiple coatings. These processes are extremely time consuming and therefore also very costly.

Another set of patents, US Pat 4,738,974; 5,690,960; 5,714,504 avoids the above-mentioned stability problem by using said acid labile benzimidazole compounds in a salt form, say in the form of a lithium, sodium, potassium, magnesium, calcium or titanium salt.

However, the above prior art method requires, for the stabilization of the benzimidazole compounds, a step of converting said compounds to such a salt form as mentioned above prior to its use in the pharmaceutical preparation.

US Patent 5626875 describes a stable oral pharmaceutical preparation containing an acid benzimidazole compound, which comprises: (a) A nucleus formed by an inert core, the acid labile benzimidazole compound, a non-alkaline inert water soluble polymer and non-alkaline reacting pharmaceutical acceptable excipients; (b) an inert non-alkaline coating disposed on said nucleus, formed by a non-alkaline water soluble polymer and non-alkaline pharmaceutical excipients, and (c) an outer layer disposed on the previous coating comprising an enteric coating.

The prior art teachings, to resolve the lack of stability of benzimidazole acid labile compounds pharmaceutical preparations, involve all a large amount of time consuming and complex steps therefore rendering such manufacturing process extremely costly.

In view of the above, the present inventors made investigations for a new cost efficient manufacturing process for the preparation of stable pharmaceutical formulations containing acid

labile benzimidazole compounds and, as a result, have completed the present invention.

Disclosure of the invention

The object of the present invention is to obtain a pharmaceutical composition comprising an acid labile benzimidazole compound that possesses excellent storage stability.

Another object of the present invention is to obtain a stable benzimidazole compound pharmaceutical composition using a simplified and/or cost effective manufacturing process involving encapsulation into hard and/or soft gelatin and/or HPMC capsules of the molten excipients with the active benzimidazole compound.

It is also an object of the present invention to obtain a pharmaceutical dosage form comprising a benzimidazole compound for oral administration.

Another object of the invention is to protect the formulation from the stomach acid juices by enteric coating the capsules.

Outline of the invention

The object of the present invention is to provide an oral enteric coated form of acid labile benzimidazole compounds, ensuring good stability and good bioavailability of said compounds and a simple and cost effective manufacturing process thereof. The new dosage form is characterized in the following way: the acid labile benzimidazole compound is formulated in a semi-solid form containing a mixture of a lipophilic solubilising and/or suspending inactive ingredients with a vitamin E derivative stabilizer. This liquids mix is then filled in to capsules. Which are thereafter enteric coated to protect the benzimidazole compound from the gastric acids.

Detailed description of the invention

Semi-solid formulation

The present invention relates to a stable, gastro-enteric semi-solid formulation of acid labile benzimidazole compound providing a good bioavailability of the drug and a cost effective manufacturing process thereof. The composition described comprises at least one lipophilic inactive ingredient and a derivate of α -tocopherol (Vitamin E) as stabilizing agent, in order to

prevent the degradation of the acid labile benzimidazole compound. The Vitamin E derivative may also acts as a co-solubilizer agent. The lipophilic excipients chosen must allow the release of the acid labile benzimidazole compound very rapidly in the proximal parts of the small intestine, in order to obtain good bioavailability of the drug.

In the preferred manufacturing process, the acid labile benzimidazole compound is added and mixed to a molten mixture of excipients. This mixture comprises the lipophilic constituents and the stabilizing agent. The temperature of the mixture is maintained sufficiently high during the whole process to maintain the mixture in a liquid state. Capsules filled with the liquid mixture are thereafter enteric coated.

The benzimidazole compound for the use in this invention have potent gastric acid antisecretory activity, gastric mucosa-protecting activity and antiulcer activity and, yet, a low toxic potential and, therefore, can find application in the treatment of peptic ulcer in mamalian animals (e.g. mouse, rat, rabbit, dog, cat and man).

The benzimidazole compounds having antiulcer activity for use in this invention includes, among specific examples, 2-[2-[3-methyl-4-(2,2,2-trifluoroethoxy)pyridyl]methylsulfinyl]benzimidazole (lansoprazole), 2-[2-[3-methyl-4-(2,2,3,3-tetrafluoropropoxy)pyridyl]methylthio] benzimidazole, 2-[(2-pyridyl)methylsulfinyl]benzimidazole (thioprazole), 2-[2-(3,5-dimethyl-4-methoxypyridyl)methylsulfinyl]-5-methoxy-1H-benzimidazole (omeprazole), 2-[2-[4-(3-methoxypropoxy)-3-methylpyridyl]methylsulfinyl]-1H-benzimidazole, 2-[2-(3,4-dimethoxy-pyridyl)methylsulfinyl]-5-difluoromethoxy-1H-benzimidazole (pantoprazole), 4-methyl-3-(2,2,2-trifluoroethoxy)-5H-pyrido[1',2':4,5][1,2,3]thiaziano[2,3-a]benzimidazol-13-ium tetrafluoroborate and so non.

The benzimidazole compounds for use in this invention may be present as racemates and/or as individual stereoisomers.

Lipophilic pharmaceutical acceptable excipients usefull for the present invention include vegetable and/or animal oils, and/or synthetic triglycerides.

The preferred oils are mono, di or triglycerides saturated or unsaturated fatty acids (e.g. palmitic acid, caprylic acid, capric acid, lauric acid, myristic acid, oleic acid, linolenic acid, laurolenic acid, etc.). Still more desirable are the triglycerides of C8 – C18 saturated fatty acids such as coconut oil (akomed®) hydrogenated soja bean oil (akosol®), synthetic triglyceride of saturated fatty acids (Gelucire 33/01).

The more desirable lipophilic pharmaceutical acceptable excipient usefull for the present invention can be, at least partially, characterized by a low hydroxyl and iodine values.

The stabilizing agent for use in this invention includes a vitamin E or Vitamin E derivative such as d or dl alpha tocopherol, d or dl alpha tocopherol acetate, d or dl alpha tocopherol acid succinate. The preferred is Vitamin E Polyethylene Glycol succinate (vitamine E TPGS®kodak).

Enteric coating

The enteric coating is applied onto the capsule after cooling. The enteric polymer may be chosen among, but are not restricted to cellulose acetate phthalate, polyvinyl acetate phthalate, Hydroxypropylmethylcellulose phthalate, co-polymerized methacrylic acid or similar compounds widely used in the pharmaceutical industry to obtain enteric coatings.

The enteric dispersion may be either an aqueous dispersion (EUDRAGIT L30D-55®, Röhm-Pharma, SURRETERIC®, Colorcon) or hydro-ethanolic dispersion and/or solutions (HP 50® and HP 55®, Shin-Etsu).

The enteric coating layer may contain a pharmaceutically acceptable plasticizer, such as for instance triacetic citric acid esters, dibutyl succinate, phthalic acid esters, propylene glycol, diethyltartarate, acetylated monoglycerides.

Thus, the preparation according to the invention consists in a stable semi-solid composition filled into capsules which are enteric coated. The capsules obtained are insoluble in acidic media but are rapidly dissolved in neutral and alkaline media.

Process

A process for the manufacturing of the oral dosage form represents a further aspect of the

invention. The simplicity and the low cost of the proposed process may indeed be considered as advantage in comparison to existing manufacturing processes. Briefly, the acid labile benzimidazole compound is incorporate to the molten mix, which contains the lipophilic inactive ingredients and the stabilizing agent. Once homogeneous, the liquid is filled into hard gelatin or HPMC capsules. The capsules are thereafter enteric-coated using a fluidized bed coater and/or any other acceptable coating equipment.

Example 1:

Acid labile benzimidazole compound (omeprazole) in mixture with Soja oil.

10g of omeprazole base is added to 190g Soja bean oil. 200mg of the mixture is introduced in hard gelatine capsules.

These capsules were stored at room temperature. After one week upon opening of said capsule the mixture color changed from white to deep brown showing degradation of omeprazole.

Example 2:

20g of omeprazole base is added to a molten mixture of 150g of Soja oil and 75g of Vitamin E Polyethylene Glycol Succinate.

245mg of the mixture is introduced in hard gelatine capsules.

The capsules were stored at room temperature and after 1 week no change in color was detected, demonstrating good stability of the acid labile benzimidazole compound.

Example 3:

20g of omeprazole base was added to a molten mixture of 150g of Soja oil and 100g of Vitamin E Polyethylene Glycol Succinate. 270mg of the mixture was introduced into hard Hydroxypropylmethylcellulose capsules. The capsules were stored at room temperature and after 1 week no change of color was observed demonstrating good stability characteristics.

Example 4:

	4a	4b	4c
Omeprazole	10	10	10
Olive Oil	97.5	67.5	67.5
Tocopherol Acetate	0	30	0
Vitamin E Polyethylene Glycol Succinate	0	0	30

Hard Gelatine fill weight [mg]: 107.5

In a beaker, add the olive oil and heat at 37°C. Start agitation, add the Vitamin E derivative and thereafter the omeprazole and continue mixing for about half hour. Fill gelatine capsules size 3 with 107.5mg of the hot mixture. The stability of these formulations were measured by observation of the color of the capsule content. It is known that omeprazole color changes from white to dark brown while degradating.

Upon storage a room temperature, the composition of formulation 4a changed color after 2 days while the formulation 4b showed some color changes after 4 days, the composition of formulation 4c did not show any color change after 1 week.

Example 5:

	5a	5b	5c
Saturated Capric and Caprilic triglycerides (akomed®)	1,462.5	1,012.5	1,012.5
Omeprazole	150	150	150
Tocopherol Acetate	0	450	0
Vitamin E Polyethylene Glycol Succinate	0	0	450

The Capsule fill weight [mg]: 107.5

The formulation of example 5 were prepared as in example 4.

The formulation stability was evaluated by the color changes of the capsule content. The

capsules were stored at room temperature and observed daily for color change.

Composition of example 5a had a light change in color after 4 days while composition of example 5b has a very light change in color after 6 days. The composition of example 5c did not show any change of color after 2 weeks of observations.

Example 6 (capsules + coating):

Omeprazole micronized	0.104g
Medium chain triglyceride	0.347g
Vitamin E TPGS	0.149g

The capsules were prepared using preparation method from example 4. Each capsule contained 20mg of omeprazole. Thereafter they were coated using a STREA1 fluidized bed coater with 20 % of dry coating of the following coating suspension:

Hypromellose phthalate (HP50)	46.8g
Talc	28.1g
Glycerol Triacetate	11.7g
Red Iron Oxide	9.4g
Ethanol	734g
Water	129g

Upon coating capsules were dried in an oven at 35°C for 8 hours. The capsules were further packaged in HDPE bottles containing 30 capsules and a 0.5g desiccant. These packaged capsules underwent a stability program at 25°C and 60% relative humidity. The percent of omeprazole versus theoretical amount was determined and was found at 101% initially, 102% after 8 months and 102% after 14 months. These results demonstrate that the formulation of example 6 is stable.

Example 7:Capsule

Omeprazole	2.45kg
Medium chain triglyceride (akomed®)	8.16kg
Vitamin E TPGS	3.50kg

In a Fryma 20 liters mixer introduce the medium chain tryglyceride and warm at 40°C under slow agitation for about 20 minutes. Add the molten vitamin E TPGS and mix for about 30 minutes maintaining temperature at 40°C.

Add omeprazole micronized and mix for an additional 30 minutes.

The hot liquid suspension is transferred to an encapsulating machine and filling hard gelatine capsules size #3 with 46mg (8mg of omeprazole) or 92mg (16mg of omeprazole) of blend is performed.

Coating

Hypromellose phtalate (HP50)	1.872kg
Talc	1.124kg
Glycerol Triacetate	0.468kg
Red Iron Oxide	0.376kg
Ethanol	29.376kg
Water	5.184kg

In a stainless steel container equipped with a Silverson High shear mixer add Ethanol and Water. Start the mixer and add slowly hypromellose phtalate. Upon complete dissolution of the hypromellose phtalate add the glycerol triacetate, talc and red iron oxide. Mix at high speed for an additional 15 minutes.

Place about 500g of capsules to be enteric coated in a fluidized bed coater STREA 1. Adjust inlet temperature at 40°C and start coating at a spray rate of about 10g per minute. Apply coating until about 1kg of the coating suspension is dispensed.

The enteric coated capsules are thereafter dried for about 8 hours in an oven at 35°C.

The capsules are packaged in High Density Polyethylene bottles containing 30 capsules and 0.5g of desiccant.

CLAIMS

1. A stable oral pharmaceutical composition comprising an acid labile benzimidazole compound in mixture with at least a lipophilic pharmaceutical acceptable excipients and at least a Vitamin E derivative.
2. A composition according to claim 1 wherein the lipophilic pharmaceutical acceptable excipients are chosen among synthetic and/or animal and/or vegetable oils and their derivatives.
3. A composition according to claim 2 wherein the synthetic and/or animal and/or vegetable oil and their derivatives may be partially and/or fully hydrogenated.
4. A composition according to claim wherein the synthetic and/or animal and/or vegetable oil has an hydroxy value less than 30 and preferentially less than 10.
5. A composition according to claim 2 wherein the synthetic and/or animal and/or vegetable oil has an Iodine value of less than 10 and preferably less than 5.
6. A composition according to claim 1 wherein the Vitamin E derivative is d,l- α -tocopherol, d, l - α -tocopherol acetate.
7. A composition according to claim 1 wherein the Vitamin E derivative is α -tocopherol polyethyleneglycol succinate.
8. A composition according to claim 1 wherein the pharmaceutical composition consist of a hard gelatine or HPMC capsule.

9. A composition according to claim 1 wherein the capsule is enteric coated.
10. A composition according to claim 1 wherein the capsule is enteric coated using an aqueous or organic solution or suspension of one of the following polymer: cellulose acetate phthalate, Hydroxypropylmethylcellulose phthalate, polyvinyl acetate phthalate, co-polymerized methacrylic acid or similar compounds.
11. A composition according to claim 1 wherein the plasticizer used in the enteric coating solution or suspension is chosen among the following: triacetic citric acid ester dibutyl succinate, phthalic acid esters, propylene glycol, diethyltartrate, acetylated monoglycerides or similar compounds.
12. A composition according to claim 1 wherein the acid labile benzimidazole compound includes lansoprazole, rabeprazole, thioroprazole, omeprazole, pantoprazole, and other proton pump inhibitors of the pyridine-benzimidazole sulfinyl family.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/IB 00/01842

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/4439 A61K9/48 A61K47/22

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS, EMBASE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 99 36060 A (TRESPIDI LAURA A ;DESAI ASHOK J (US); MEYER GLENN A (US); CLARK CH) 22 July 1999 (1999-07-22) page 3, line 19 -page 4, line 6 page 5, last line page 8, line 9 - line 20 page 9, line 19 - line 26 page 10, line 4 - line 13; claims 1,8-11,15,28,29; example 39 ---	1-12
A	EP 0 712 631 A (BIOGAL GYOGYSZERGYAR) 22 May 1996 (1996-05-22) page 3, line 8 - line 15 page 3, line 27 - line 30 page 4, line 9 - line 13; claims 1,7,8; examples --- -/--	1-12



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

Z document member of the same patent family

Date of the actual completion of the international search

26 March 2001

Date of mailing of the international search report

03/04/2001

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Marttin, E

INTERNATIONAL SEARCH REPORT

International Application No

PCT/IB 00/01842

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>US 5 045 321 A (MAKINO TADASHI ET AL) 3 September 1991 (1991-09-03) cited in the application column 1, paragraph 1; examples 2,4; table 1 column 1, paragraph 4 column 2, line 7 - line 18 column 9, line 32 - line 44 column 10, line 3 - line 51; claim 1 -----</p>	1-12

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/IB 00/01842

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9936060 A	22-07-1999	AU 2117399 A EP 1049459 A NO 20003698 A	02-08-1999 08-11-2000 12-09-2000
EP 0712631 A	22-05-1996	HU 215966 B CA 2145242 A CZ 9501054 A DE 19543271 A GB 2295546 A, B IT MI952411 A PL 311430 A SI 9500350 A SK 54495 A US 5583105 A	28-07-1999 22-05-1996 17-07-1996 05-06-1996 05-06-1996 21-05-1996 27-05-1996 30-06-1996 05-02-1997 10-12-1996
US 5045321 A	03-09-1991	BG 61202 B CA 1327010 A CA 1338377 A CA 1338399 A DE 3750431 D DE 3750431 T DE 3751845 D DE 3751845 T DE 3780045 A DE 3780045 T EP 0237200 A EP 0423748 A EP 0446961 A HK 188195 A HK 1002021 A JP 1893359 C JP 3038247 B JP 62277322 A SG 50619 A US 5433959 A US 6017560 A US 6123962 A US 5639478 A US 5093132 A US 5246712 A US 5879708 A	28-02-1997 15-02-1994 11-06-1996 18-06-1996 29-09-1994 22-12-1994 25-07-1996 28-11-1996 06-08-1992 24-12-1992 16-09-1987 24-04-1991 18-09-1991 22-12-1995 24-07-1998 26-12-1994 10-06-1991 02-12-1987 20-07-1998 18-07-1995 25-01-2000 26-09-2000 17-06-1997 03-03-1992 21-09-1993 09-03-1999